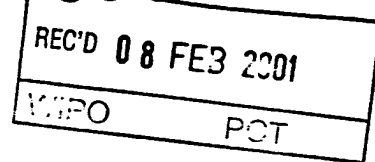


PCT



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



15

Applicant's or agent's file reference HI-PCT-1	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/08004	International filing date (day/month/year) 22/10/1999	Priority date (day/month/year) 28/10/1998
International Patent Classification (IPC) or national classification and IPC A61K31/439		
Applicant IKONOMIDOU, Hrissanthi		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 03/05/2000	Date of completion of this report 05.02.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Simm, M.D. Telephone No. +49 89 2399 7411 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/08004

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-21 as originally filed

Claims, No.:

1-37 as originally filed

Drawings, sheets:

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/08004

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-37.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-37.

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims see sep. sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/08004

	No:	Claims	
Inventive step (IS)	Yes:	Claims	see sep. sheet
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-34

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/08004

Re Item I

Basis of the opinion

Reference is made to the following documents:

- D1: S. BEN-ELIYAHU: 'The NMDA receptor antagonist MK-801 blocks nonopioid stress induced analgesia and decreases tumor metastasis in the rat.'
PROCEEDINGS OF THE WESTERN PHARMACOLOGY SOCIETY, vol. 36,
1993, pages 293-298
- D2: K. IGARASHI: 'Antagonist properties of polyamines and bis(ethyl)polyamines at N-methyl-D-aspartate receptors.' JOURNAL OF PHARMACOLOGY AND
EXPERIMENTAL THERAPEUTICS, vol. 272, no. 3, 1995, pages 1101-1109

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

No International Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT). The opinion is limited to the inventive concept: use of glutamate antagonists for the treating cancer, and to the examples.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The opinion expressed as to novelty and inventive step only refers to matter for which an international search report has been drawn up (see also Item III).

Novelty (Art. 32(2) PCT).

The general inventive concept of the present application: the use of glutamate

antagonists for the treating cancer is not novel.

D1 discloses the antitumoral properties of MK-801, which is a NMDA receptor antagonist and one of the three glutamate antagonists used in the examples of the present application (see page 16 fifth paragraph in the present application (see Introduction and Discussion).

D2 discloses that Bis(ethyl)polyamines, which have marked antagonist effects on NMDA receptors, have potent antiproliferative activity *in vitro* and antitumor activity in animal models *in vivo* and that some of these compounds are being considered for further development in clinical trials as antitumor agents (see abstract and page 1108, left column in D2).

Thus, the use of inhibitors of the interaction of glutamate with the NMDA channel complex for the treatment of cancer is not novel. However, the use of inhibitors of the interaction of glutamate with the AMPA and KA receptor complexes is novel.

Inventive Step (Art. 33(3) PCT).

D1 teaches that excitatory amino acids (EAA) are implicated in mediating stress induced analgesia (SIA) and that immunity and tumor development have been shown to be affected by a variety of stressors. Furthermore, D1 discloses the antitumoral properties of MK-801, which is a NMDA receptor antagonist.

Thus, from D1 it is known that the EAA are implicated in tumor development and therefore can be deduced that NMDA receptor antagonist have an antitumoral effect.

Thus, the general inventive concept of the present application: the use of glutamate antagonists for treating cancer does not involve an inventive step.

However, the use of inhibitors of the interaction of glutamate with the AMPA and KA receptor complexes is neither disclosed nor suggested in the cited prior art. Thus, these are considered inventive.

Industrial Applicability (Art. 33(4) PCT).

For the assessment of the present claims 1-34 on the question whether they are

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/08004

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1 (a)(ii) PCT, the relevant background art disclosed in the documents D1-D2 , is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

The claims lack support by the description (Art. 6 PCT). The Examples of the present application show the antitumoral effects of two different AMPA antagonists and the NMDA antagonist MK801. It appears that the general inventive concept and the claims, which refer to the use of practically any substance which can affect the concentration of glutamate, do not correspond to the contribution to the art shown in the examples.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference HI-PCT-1	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 99/08004	International filing date (day/month/year) 22/10/1999	(Earliest) Priority Date (day/month/year) 28/10/1998
Applicant IKONOMIDOU, Hrisanthi		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 June 2000 (06.06.00)	
International application No. PCT/EP99/08004	Applicant's or agent's file reference HI-PCT-1
International filing date (day/month/year) 22 October 1999 (22.10.99)	Priority date (day/month/year) 28 October 1998 (28.10.98)
Applicant IKONOMIDOU, Hrisanthi	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
03 May 2000 (03.05.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer <p style="text-align: center;">C. Villet</p> Telephone No.: (41-22) 338.83.38
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/08004

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/439 A61K31/5513 A61K31/498 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. BEN-ELIYAHU: "The NMDA receptor antagonist MK-801 blocks nonopioid stress induced analgesia and decreases tumor metastasis in the rat." PROCEEDINGS OF THE WESTERN PHARMACOLOGY SOCIETY, vol. 36, 1993, pages 293-298, XP002106887 the whole document	1-36
X	N. SEILER: "Polyamine sulfonamides with NMDA antagonist properties are potent calmodulin antagonists and cytotoxic agents." INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, vol. 30, no. 3, March 1998 (1998-03), pages 393-406, XP002089917 the whole document	1-36

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

7 February 2000

Date of mailing of the international search report

14/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Orviz Diaz, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/08004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. IGARASHI: "Antagonist properties of polyamines and bis(ethyl)polyamines at N-methyl-D-aspartate receptors." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 272, no. 3, 1995, pages 1101-1109, XP002106888 the whole document ----	1-36
X	I. CHAUDIEU: "D-Aspartic Beta Hydroxymate (DAH), an Antitumoral Drug, Acts on N-Methyl-D-Aspartate Receptors in Rat Brain." J. NEUROCHEM., vol. 61, no. suppl, 1993, page S255 XP002106889 abstract ----	1-36
X	K. YAMADA: " Clinical and experimental studies on the antileukemic action of L-asparaginase" COLLOQ. INT. CENT. NAT. RECH. SCI., no. 197, 1971, pages 311-322, XP002106890 the whole document ----	1-36
X	US 4 885 171 A (SURENDRA SEHGAL N ET AL) 5 December 1989 (1989-12-05) the whole document ----	1-37
A	EP 0 778 023 A (AMERICAN HOME PROD) 11 June 1997 (1997-06-11) the whole document ----	1-37
X	EP 0 432 994 A (OLNEY JOHN WILLIAM) 19 June 1991 (1991-06-19) the whole document -----	36,37

INTERNATIONAL SEARCH REPORT

international application No.

PCT/EP 99/08004

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

In view of the extremely large number of compounds mentioned in the claims, many of them characterised only by a generic structural definition, a complete search is not possible. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found for only a very small proportion of the compounds claimed. Consequently, the search had to be limited to the general inventive idea (use of glutamate antagonists for the manufacture of a medicament for treating cancer) and to the specific compounds used in the pharmacological examples.

Since the use of some of these compounds (MK 801, polyamines, rapamycin) for treating cancer is already known, the use of each of the compounds claimed would represent a separate invention. However, an objection of lack of unity has not been raised, because the documents cited in the Search Report, which were retrieved during the restricted search described in the previous paragraph, already cover the general inventive idea and some of the compounds used in the pharmacological examples, like MK 801 (see Proc. West. Pharmacol. Soc. 36:293-298, 1993).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/08004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4885171 A	05-12-1989	US 5206018 A	27-04-1993
		US 5066493 A	19-11-1991
		BE 877700 A	14-01-1980
		JP 55073616 A	03-06-1980
		ZA 7905449 A	26-11-1980
EP 0778023 A	11-06-1997	AU 700653 B	14-01-1999
		AU 7417896 A	12-06-1997
		BR 9605895 A	18-08-1998
		CA 2192298 A	08-06-1997
		CN 1159915 A	24-09-1997
		CZ 9800064 A	17-06-1998
		CZ 9603544 A	18-03-1998
		HU 9603370 A	28-05-1997
		IL 119778 A	14-07-1999
		JP 9183727 A	15-07-1997
		NO 965238 A	09-06-1997
		SK 154796 A	10-09-1997
EP 0432994 A	19-06-1991	US 5039528 A	13-08-1991